miRComb - An R package for analyzing miRNA-mRNA interactions

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1 Workflow

This package provides a workflow for miRNA target analysis. Data about the miRNA databases is stores in a separate package –`miRData`–, which is is automatically loaded with `miRComb`.
The main workflow of the package is represented in the following figure. We start from two datasets, where correlations are computed. Then they are combined with a database –microCosm or others– and a functional analysis of the results can be performed.

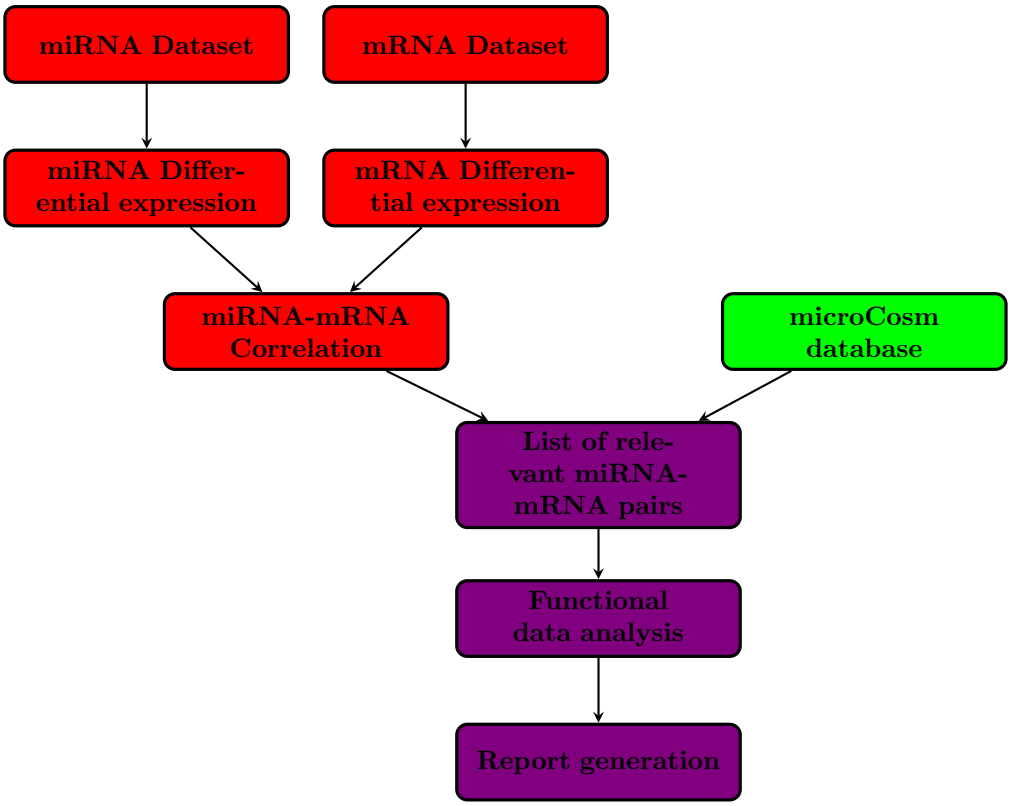

Figure 1: Outline of the pipeline.

2 Data format

We need the expression matrix for the miRNA and mRNA. The file format must be as follows:

- Expression matrices: a `matrix` with normalized data (preferably normalized log2 expression values). Columns should correspond to samples and Rows to probesets. Column names and Row names will be used as sample names and probe names respectively.
- Phenotypical information: a `data.frame`. Rows corresponding to sample names (must match with the Column names from the expression matrices). Columns with the desired combinations to test must be filled with 0 and 1. For example:

```
    group DvH
H_1     H   0
H_2     H   0
H_3     H   0
D_1     D   1
D_2     D   1
D_3     D   1
D_4     D   1
D_5     D   1
D_6     D   1
D_7     D   1
D_8     D   1
D_9     D   1
```

3 Creating the `corObject`

A `corObject` contains the following slots:

- `dat.miRNA`: miRNA matrix expression

- `dat.mRNA`: mRNA matrix expression
- `pheno.miRNA`: phenotypical miRNA information
- `pheno.mRNA`: phenotypical mRNA information
- `cor`: correlation matrix
- `pval`: correlation p value matrix
- `net`: a dataframe that can be used for cytoscape
- `diffexp.miRNA`: differential expression analysis from miRNA data
- `diffexp.mRNA`: differential expression analysis from mRNA data
- `sig.miRNA`: significant miRNAs
- `sig.mRNA`: significant mRNAs
- `info`: information of the tests performed

However, not all slots are mandatory for creating a simple `corObject`. A `corObject` can be created from the matrix expressions and phenotypical information. Further slots can be filled with specific functions. We can begin with the data provided as example (the data has been adapted from [1]):

```
> library(miRComb)
> data(miRNA)
> data(mRNA)
> data(pheno.miRNA)
> data(pheno.mRNA)
```

To create the `corObject`:

```
> data.obj<-new("corObject",dat.miRNA=as.matrix(miRNA),dat.mRNA=as.matrix(mRNA),
+         pheno.miRNA=pheno.miRNA,pheno.mRNA=pheno.mRNA)
```

4 Analysis

4.1 Exploratory analysis

Some plots are allowed to explore the data. For example we can plot the distances between samples of the mRNA dataset (Figure 2).

```
> plotCordist(data.obj,subset="mRNA",type="dist")
```

After this exploratory analysis, it is also possible to remove some samples and/or miRNAs/mRNAs. In this case we must indicate which sample and in which dataset we want to remove. The sample will be removed from the corresponding expression matrix and phenotypical dataframe. It is also possible to remove all the samples except for the selected ones. The procedures would be:

```
> #data.obj<-remove.samp(data.obj,"mRNA",c("D_4"))        #remove D_4 from the mRNA dataset
> #data.obj<-remove.samp(data.obj,"miRNA",genes="hsa-miR-21",keep=TRUE)        #keep only hsa-miR-21
```

Boxplots of the expression can also be plotted (Figure 3):

```
> boxplotSamples(data.obj,subset="mRNA")
```

PCA plots are also available (Figure 4, and `plot3d` function plots a PCA in 3 dimensions):

```
> plotPca(data.obj,subset="mRNA")
```

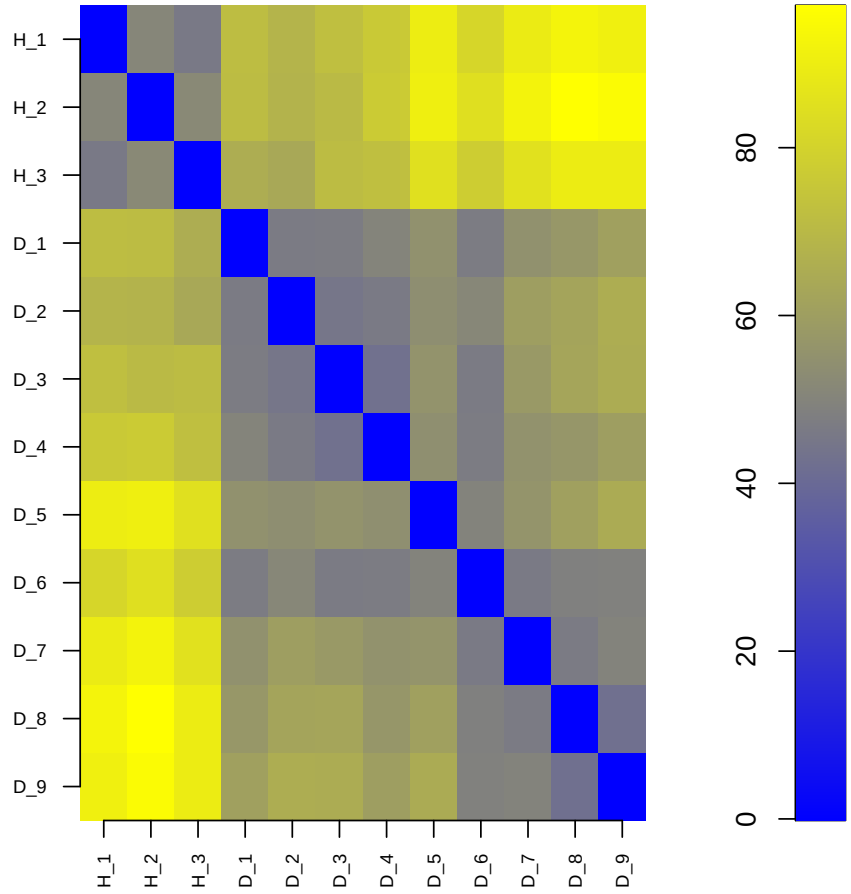

Figure 2: Plot of the distance between the samples of the mRNA dataset.

4.2 Differential expression

We can add FoldChange information to the net from the differential expression slot. If this slot is not available, we can create it (indicating the column with the desired combination, in this case *Disease* (D) versus *Healthy* (H), column `DvH` (see Section 2 to see the format of the column)):

```
> data.obj<-addDiffexp(data.obj,"miRNA",classes="DvH",method.dif="limma")
> data.obj<-addDiffexp(data.obj,"mRNA",classes="DvH",method.dif="limma")
```

Plot a heatmap of the top miRNA or mRNA (sorted by p value) (Figure 5):

```
> plotHeatmap(data.obj,"mRNA")
```

Moreover, we can obtain specific subsets, for example those genes with FoldChange greater than 10, a corrected p value less than 0.05 and specifically upregulated:

```
> selSubsetExprs(data.obj,"mRNA",FC=10,up=TRUE,adj.pval=0.05)
```

```
               FC logratio   meanExp         pval     adj.pval
ANAPC16  35.75054 5.159893  9.454859 7.875760e-08 4.510663e-05
CLPX     10.63198 3.410338  7.468754 7.785881e-09 1.131947e-05
DUSP19   33.55178 5.068318  7.241382 3.372921e-06 3.006991e-04
FOXI1    56.70853 5.825494  8.014330 1.110212e-06 1.745830e-04
KPNA1    42.30617 5.402796  7.394774 9.421473e-07 1.709220e-04
MYL7     15.74098 3.976453  8.024974 2.291436e-05 8.545174e-04
NDOR1    14.57899 3.865819  6.629975 5.064322e-04 6.276438e-03
SLC7A2   15.26068 3.931748  7.351221 2.449509e-04 3.910111e-03
```

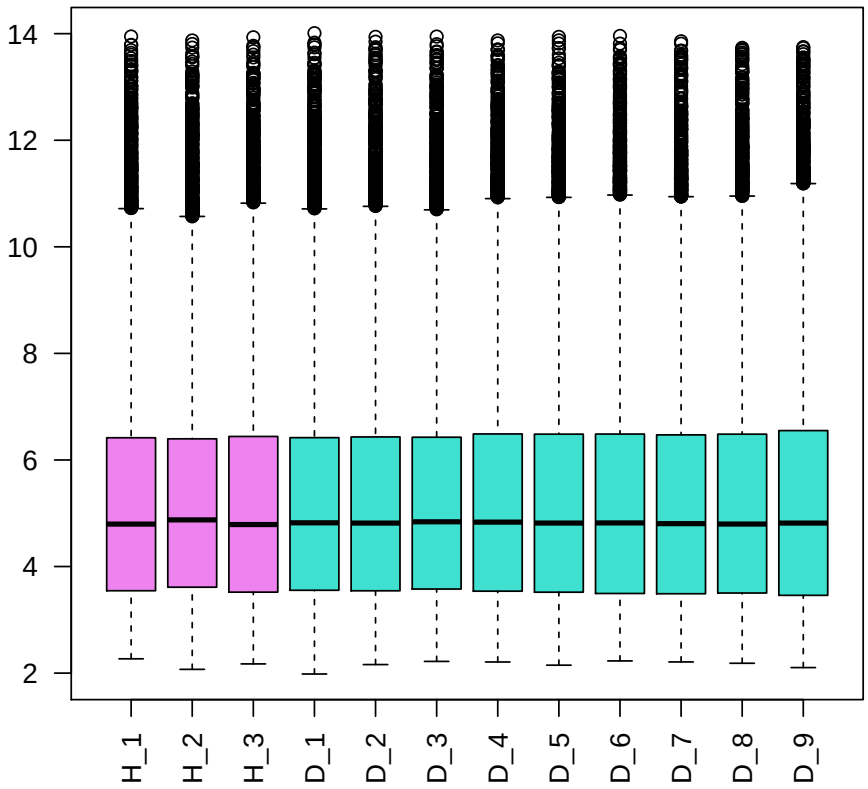

Figure 3: Boxplot of the mRNA samples.

```
SYT15     32.05831 5.002627  7.561346 1.629203e-06 1.961270e-04
THRAP3    14.04741 3.812232  6.822951 9.593953e-06 5.136706e-04
TMC1      22.41579 4.486443 10.093581 1.545755e-06 1.909462e-04
VWDE     241.33797 7.914911 10.807522 5.753775e-11 5.437318e-07
```

The same options can be used to add this information to the `corObject`. **The significant miRNAs and mRNAs added in this step will be used in correlation step.**

```
> data.obj<-addSig(data.obj,"mRNA",adj.pval=0.05,FC=1.5)
> data.obj<-addSig(data.obj,"miRNA",adj.pval=0.05)
```

If you have a specific list of miRNAs and/or mRNAs that you want to test, you should add them there in this step, for example:

```
> #data.obj<-addSig(data.obj,"miRNA",manual=c("hsa-miR-21","hsa-miR-21*,hsa-miR-200c"))
```

4.3 Correlation

The next step is to compute the correlation between the two matrices, the alternative hypothesis is `"less"` because we are interested only on negative correlations:

```
> data.obj<-addCorrelation(data.obj,alternative="less")
```

```
Correlating miRNA and mRNA
```

At this moment, the slots `cor` and `pval` have been filled. The column names are the mRNAs selected by `add.sig`, and the row names are the miRNAs selected by `add.sig` also:

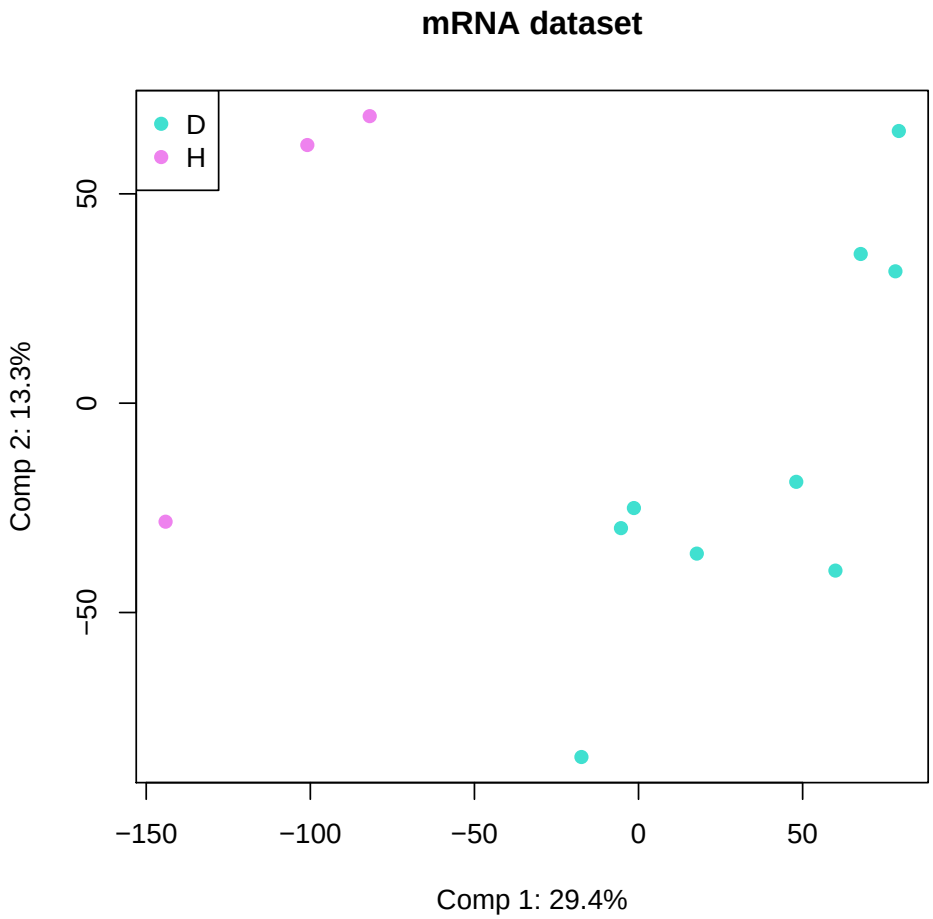

Figure 4: Principal Components Analysis (based on the correlation matrix) of the mRNA samples.

```
> data.obj@cor[1:3,1:3]

                  A2ML1      ABCC6      ABCD3
hsa-miR-107  -0.8616698 -0.7886117  0.5100627
hsa-miR-1208 -0.9231799 -0.8446258  0.7978511
hsa-miR-1231  0.9492489  0.8967782 -0.7377228

> data.obj@pval[1:3,1:3]

                    A2ML1        ABCC6       ABCD3
hsa-miR-107  1.573829e-04 0.0011512207 0.954885976
hsa-miR-1208 9.250455e-06 0.0002730272 0.999063814
hsa-miR-1231 9.999988e-01 0.9999612867 0.003084055
```

If `add.sig` was set to `NULL`, all the miRNAs and/or mRNAs are used, respectively.

4.3.1 Diagnostic plots

It is also possible to plot the correlation for each pair (Figure 8) and some diagnostic plots for the linear correlation (Figure 7):

```
> plotCorrelation(data.obj,miRNA="hsa-miR-107",mRNA="A2ML1",type="cor",
+     col.color="group",sample.names=TRUE)
> plotCorrelation(data.obj,miRNA="hsa-miR-107",mRNA="A2ML1",type="residuals")
```

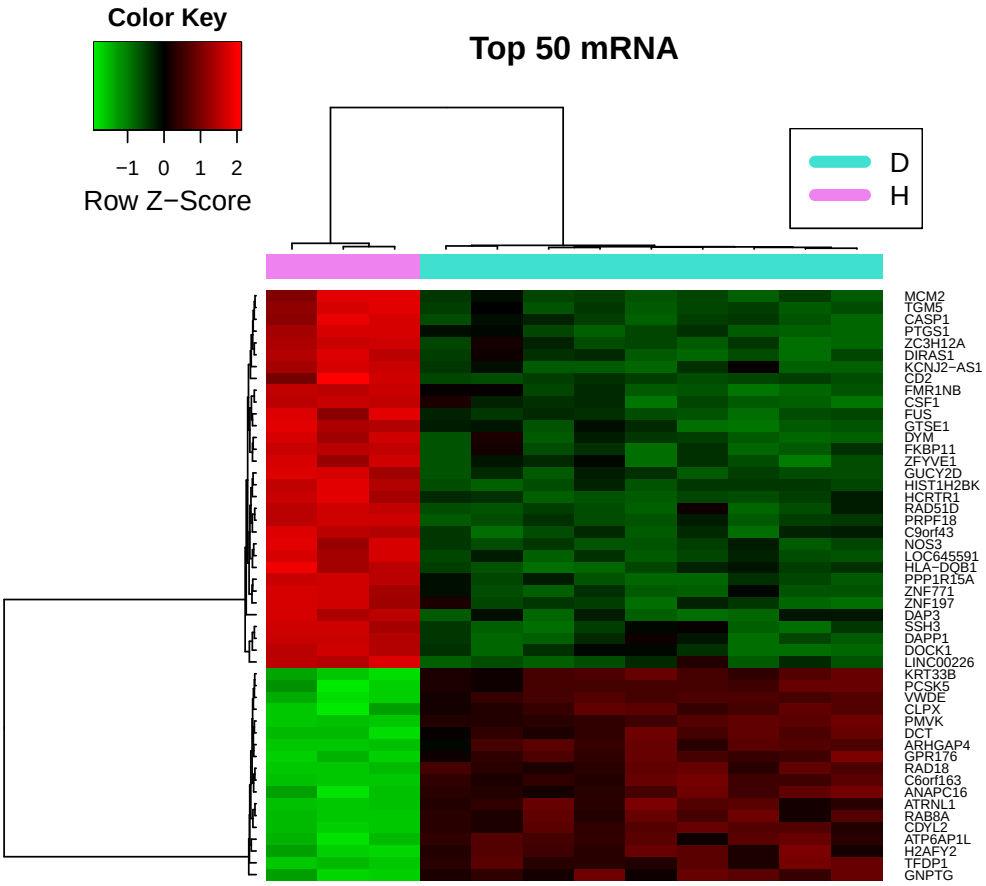

Figure 5: Heatmap of top 50 mRNAs, sorted by p value.

4.4 Organize the pairs in rows

These slots can be used to create another slot, which is called `net`. This slot contains a `data.frame` where each row represents a specific miRNA-mRNA pair, and each column contains information relevant to the pair, the name of the table refers to Cytoscape software, as this format can be easily imported to it [2]. In this step of the analysis the columns are: miRNA, mRNA, correlation coefficient and p value; other columns will be added in further steps.

```
> data.obj<-addNet(data.obj)

Converting to net

> head(data.obj@net)

                          miRNA   mRNA        cor         pval
hsa-miR-107:A2ML1  hsa-miR-107  A2ML1 -0.8616698 0.0001573829
hsa-miR-107:ABCC6  hsa-miR-107  ABCC6 -0.7886117 0.0011512207
hsa-miR-107:ABCD3  hsa-miR-107  ABCD3  0.5100627 0.9548859759
hsa-miR-107:ABHD12 hsa-miR-107 ABHD12  0.9178376 0.9999871718
hsa-miR-107:ABHD4  hsa-miR-107  ABHD4 -0.7378162 0.0030790960
hsa-miR-107:ABI1   hsa-miR-107   ABI1 -0.5795687 0.0241310206
```

4.5 Foldchanges

As optional, we add the FoldChange information of the `diffexp.miRNA` and `diffexp.mRNA` slots to the `net` slot:

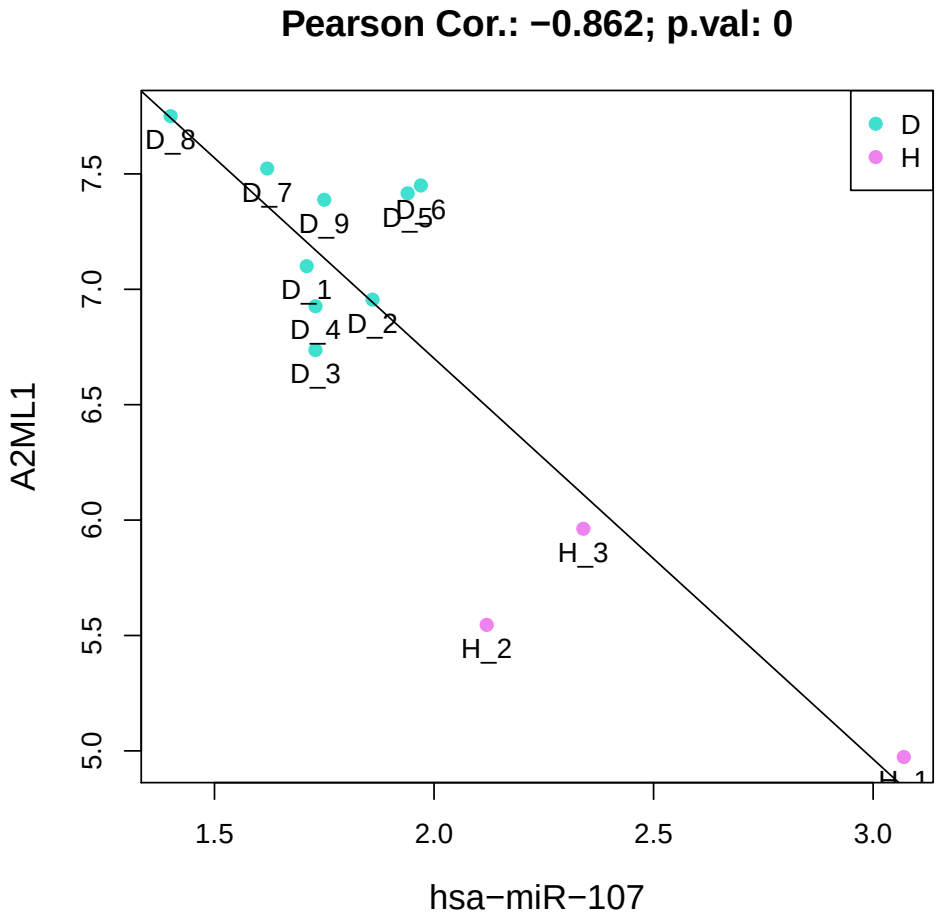

Figure 6: Plot of the correlation of one miRNA (*hsa-miR-107*) and one mRNA (*A2ML1*). Horizontal and vertical axis represent the (log2-)expression values (see Section 2) of the miRNA and mRNA, respectively.

```
> data.obj<-addFoldchanges(data.obj)
> head(data.obj@net)
```

```
                         miRNA    mRNA        cor         pval logratio.miRNA
hsa-miR-107:A2ML1  hsa-miR-107   A2ML1 -0.8616698 0.0001573829     -0.7644444
hsa-miR-107:ABCC6  hsa-miR-107   ABCC6 -0.7886117 0.0011512207     -0.7644444
hsa-miR-107:ABCD3  hsa-miR-107   ABCD3  0.5100627 0.9548859759     -0.7644444
hsa-miR-107:ABHD12 hsa-miR-107  ABHD12  0.9178376 0.9999871718     -0.7644444
hsa-miR-107:ABHD4  hsa-miR-107   ABHD4 -0.7378162 0.0030790960     -0.7644444
hsa-miR-107:ABI1   hsa-miR-107    ABI1 -0.5795687 0.0241310206     -0.7644444
                   logratio.mRNA meanExp.miRNA meanExp.mRNA
hsa-miR-107:A2ML1      1.7556491      1.936667     6.810779
hsa-miR-107:ABCC6      0.8767317      1.936667     5.806870
hsa-miR-107:ABCD3     -0.8775035      1.936667     5.329774
hsa-miR-107:ABHD12    -1.1404364      1.936667     5.685076
hsa-miR-107:ABHD4      1.3967358      1.936667     4.653627
hsa-miR-107:ABI1       1.8646091      1.936667     7.268884
```

4.6 Adding targets information

At this moment, two databases are provided, but if it is necessary we can add more (see `?add.database`):

```
> data(microCosm_v5_18)
> data(targetScan_v6.2_18)
```

The function to add the database(s) information is (this step can take a while):

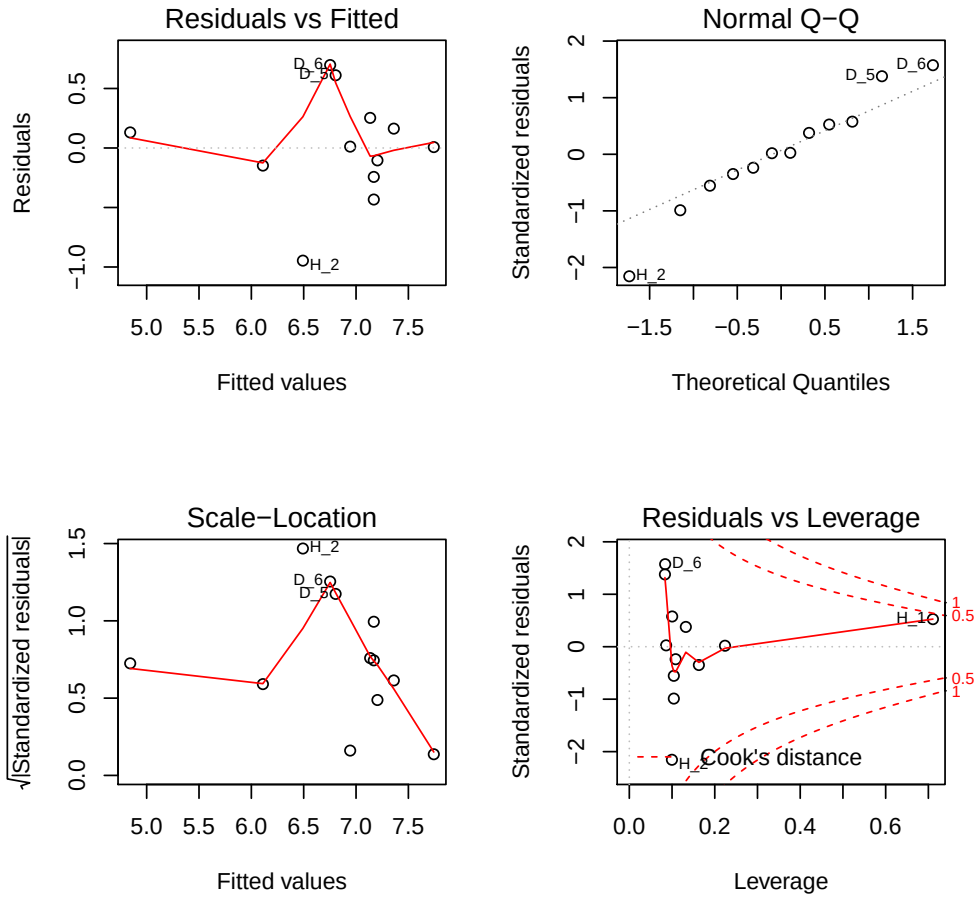

Figure 7: Diagnostic plot for the linear regression between *hsa-miR-107* and *A2ML1* (see Figure 8).

```
> data.obj<-addDatabase(data.obj,database=c("microCosm_v5_18","targetScan_v6.2_18"))

Intersecting with database
 microCosm_v5_18 database chosen
 targetScan_v6.2_18 database chosen

> head(data.obj@net)

                          miRNA    mRNA        cor         pval logratio.miRNA
hsa-miR-107:A2ML1  hsa-miR-107   A2ML1 -0.8616698 0.0001573829     -0.7644444
hsa-miR-107:ABCC6  hsa-miR-107   ABCC6 -0.7886117 0.0011512207     -0.7644444
hsa-miR-107:ABCD3  hsa-miR-107   ABCD3  0.5100627 0.9548859759     -0.7644444
hsa-miR-107:ABHD12 hsa-miR-107  ABHD12  0.9178376 0.9999871718     -0.7644444
hsa-miR-107:ABHD4  hsa-miR-107   ABHD4 -0.7378162 0.0030790960     -0.7644444
hsa-miR-107:ABI1   hsa-miR-107    ABI1 -0.5795687 0.0241310206     -0.7644444
                   logratio.mRNA meanExp.miRNA meanExp.mRNA dat.microCosm_v5_18
hsa-miR-107:A2ML1      1.7556491      1.936667     6.810779                    0
hsa-miR-107:ABCC6      0.8767317      1.936667     5.806870                    0
hsa-miR-107:ABCD3     -0.8775035      1.936667     5.329774                    0
hsa-miR-107:ABHD12    -1.1404364      1.936667     5.685076                    1
hsa-miR-107:ABHD4      1.3967358      1.936667     4.653627                    0
hsa-miR-107:ABI1       1.8646091      1.936667     7.268884                    0
                   dat.targetScan_v6.2_18 dat.sum
hsa-miR-107:A2ML1                       0       0
hsa-miR-107:ABCC6                       0       0
hsa-miR-107:ABCD3                       0       0
```

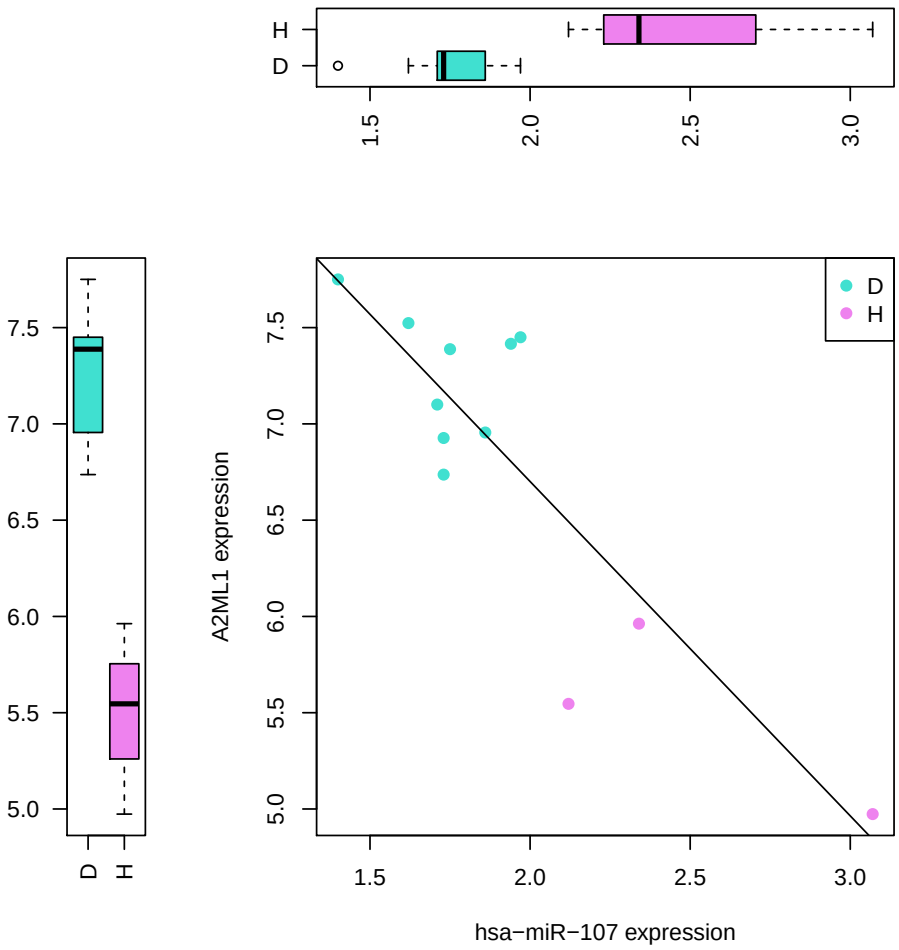

Figure 8: Plot of the correlation of one miRNA (*hsa-miR-107*) and one mRNA (*A2ML1*). Horizontal and vertical axis represent the (log2-)expression values (see Section 2) of the miRNA and mRNA, respectively.

```
hsa-miR-107:ABHD12                0       1
hsa-miR-107:ABHD4                 0       0
hsa-miR-107:ABI1                  0       0
```

And we can see that some columns have been added:

- One column for each database, with the name: `dat.`*`database_name`*. 1 means that the miRNA-mRNA pair has been found as predicted in that database, 0 that the miRNA-mRNA pair is not predicted.
- The column `dat.sum`, it reports how many times that miRNA-mRNA pair has been found in the used databases.

4.7 *P* value correction

We can add a column with the corrected p value as follows. This step is important for controlling the Type I error of the correlations:

```
> data.obj<-correctPval(data.obj, pval="pval",method.adj="BH")

Correcting p.values

> head(data.obj@net)

                        miRNA   mRNA        cor         pval logratio.miRNA
hsa-miR-107:A2ML1  hsa-miR-107  A2ML1 -0.8616698 0.0001573829     -0.7644444
hsa-miR-107:ABCC6  hsa-miR-107  ABCC6 -0.7886117 0.0011512207     -0.7644444
```

```
hsa-miR-107:ABCD3  hsa-miR-107  ABCD3  0.5100627 0.9548859759     -0.7644444
hsa-miR-107:ABHD12 hsa-miR-107 ABHD12  0.9178376 0.9999871718     -0.7644444
hsa-miR-107:ABHD4  hsa-miR-107  ABHD4 -0.7378162 0.0030790960     -0.7644444
hsa-miR-107:ABI1   hsa-miR-107   ABI1 -0.5795687 0.0241310206     -0.7644444
                   logratio.mRNA meanExp.miRNA meanExp.mRNA dat.microCosm_v5_18
hsa-miR-107:A2ML1      1.7556491      1.936667     6.810779                    0
hsa-miR-107:ABCC6      0.8767317      1.936667     5.806870                    0
hsa-miR-107:ABCD3     -0.8775035      1.936667     5.329774                    0
hsa-miR-107:ABHD12    -1.1404364      1.936667     5.685076                    1
hsa-miR-107:ABHD4      1.3967358      1.936667     4.653627                    0
hsa-miR-107:ABI1       1.8646091      1.936667     7.268884                    0
                   dat.targetScan_v6.2_18 dat.sum    adj.pval
hsa-miR-107:A2ML1                       0       0 0.003339896
hsa-miR-107:ABCC6                       0       0 0.007664571
hsa-miR-107:ABCD3                       0       0 0.999999967
hsa-miR-107:ABHD12                      0       1 0.999999967
hsa-miR-107:ABHD4                       0       0 0.013097872
hsa-miR-107:ABI1                        0       0 0.055137516
```

4.8 Interaction score

Finally, a score can be added to each interaction. This score is related to both logratios and it is aimed to reflect the possible *biological relevance* of the miRNA (higher score means that both miRNA and mRNA are highly deregulated in that disease).

$$\text{score} = -2(\text{logratio}_{\text{miRNA}} \cdot \text{logratio}_{\text{mRNA}})$$

```
> data.obj<-addScore(data.obj)
> head(data.obj@net)
```

```
                       miRNA   mRNA        cor         pval logratio.miRNA
hsa-miR-107:A2ML1  hsa-miR-107  A2ML1 -0.8616698 0.0001573829     -0.7644444
hsa-miR-107:ABCC6  hsa-miR-107  ABCC6 -0.7886117 0.0011512207     -0.7644444
hsa-miR-107:ABCD3  hsa-miR-107  ABCD3  0.5100627 0.9548859759     -0.7644444
hsa-miR-107:ABHD12 hsa-miR-107 ABHD12  0.9178376 0.9999871718     -0.7644444
hsa-miR-107:ABHD4  hsa-miR-107  ABHD4 -0.7378162 0.0030790960     -0.7644444
hsa-miR-107:ABI1   hsa-miR-107   ABI1 -0.5795687 0.0241310206     -0.7644444
                   logratio.mRNA meanExp.miRNA meanExp.mRNA dat.microCosm_v5_18
hsa-miR-107:A2ML1      1.7556491      1.936667     6.810779                    0
hsa-miR-107:ABCC6      0.8767317      1.936667     5.806870                    0
hsa-miR-107:ABCD3     -0.8775035      1.936667     5.329774                    0
hsa-miR-107:ABHD12    -1.1404364      1.936667     5.685076                    1
hsa-miR-107:ABHD4      1.3967358      1.936667     4.653627                    0
hsa-miR-107:ABI1       1.8646091      1.936667     7.268884                    0
                   dat.targetScan_v6.2_18 dat.sum    adj.pval     score
hsa-miR-107:A2ML1                       0       0 0.003339896  2.684192
hsa-miR-107:ABCC6                       0       0 0.007664571  1.340425
hsa-miR-107:ABCD3                       0       0 0.999999967 -1.341605
hsa-miR-107:ABHD12                      0       1 0.999999967 -1.743601
hsa-miR-107:ABHD4                       0       0 0.013097872  2.135454
hsa-miR-107:ABI1                        0       0 0.055137516  2.850780
```

4.9 Save the results

It is possible to output the results to text files and explore them with other tools if desired (for example *excel* or *libreoffice*).

```
> writeCsv(data.obj,"results_today.csv",pval.corrected=1)
```

These networks can also be opened by cytoscape (v2.x), by indicating the pathway of the folder which contains the `cytoscape.jar` file:

```
> #openCytoscape(data.obj,p.cutoff=0.0001,cytoscape.folder="/home/mvila/Cytoscape_v2.8.3")
```

5 Functional analysis

5.1 Most targeted miRNAs or mRNAs

A table showing the number of targets for each miRNA (or a table showing the number of miRNAs that are targeting a specific mRNA) can be obtained (with the option `names=TRUE`, the names of the targets are also reported). All the miRNA/mRNA are plotted and displayed here, even if they have no targets (Figure 9).

```
> topTable(data.obj,"miRNA",names=FALSE,pval.cutoff=0.05)[1:20]
```

```
    hsa-miR-544      hsa-miR-107  hsa-miR-516a-3p hsa-miR-4659a-3p
             54               49               49               44
    hsa-miR-184  hsa-miR-548a-3p   hsa-miR-628-5p    hsa-miR-548ah
             43               40               40               37
   hsa-miR-190b   hsa-miR-127-5p   hsa-miR-518c*   hsa-miR-542-5p
             35               34               33               32
   hsa-miR-30a*      hsa-miR-523   hsa-miR-548aj     hsa-miR-548f
             28               27               27               26
 hsa-miR-218-1*     hsa-miR-4673      hsa-miR-610     hsa-miR-4251
             24               22               22               21
```

This information can also be represented with a barplot (Figure 9):

```
> topTable(data.obj,"miRNA",names=TRUE,pval.cutoff=0.05,plot=TRUE)
```

5.2 Network

We can draw a network (Figure 10) with the following procedure. We need to give a p value cutoff (this p value refers to the corrected p value) and a minimum number of occurrences on the theoretical databases (`dat.sum`, see Section 4.6):

```
> plotNetwork(data.obj,pval.cutoff=0.01,dat.sum=1)
```

A bigger picture (Figure 11):

```
> plotNetwork(data.obj,pval.cutoff=0.05,names=FALSE)
```

A picture of the miRNA with more targets (Figure 12):

```
> hub<-names(topTable(data.obj,"miRNA"))[1]
> plotNetwork(data.obj,pval.cutoff=0.05,names=TRUE,sub.miRNA=hub,vertex.cex="interact.table")
```

***Any of these networks can be opened with Cytoscape using the function `openCytoscape`.**

5.3 Gene Ontology analysis

It is possible to select the mRNA of the pairs according to the combined p value and perform a GO enrichment analysis (reference genes are the whole human genome).

```
> GO.results<-GOanalysis(data.obj,type="GO",ontology="BP")
```

We can also compute the GO of a specific miRNA:

```
> #data.obj<-GOanalysis(data.obj,type="GO",ontology="BP",sub.miRNA="hsa-miR-516a-3p")
> #GO.results<-data.obj@GO.results[["GO:BP"]]
> #GO.results[which(GO.results$Pvalue<0.1),"Term"]
```

6 Summary

Finally, a summary of the methods used can be obtained:

```
> summary(data.obj)
```

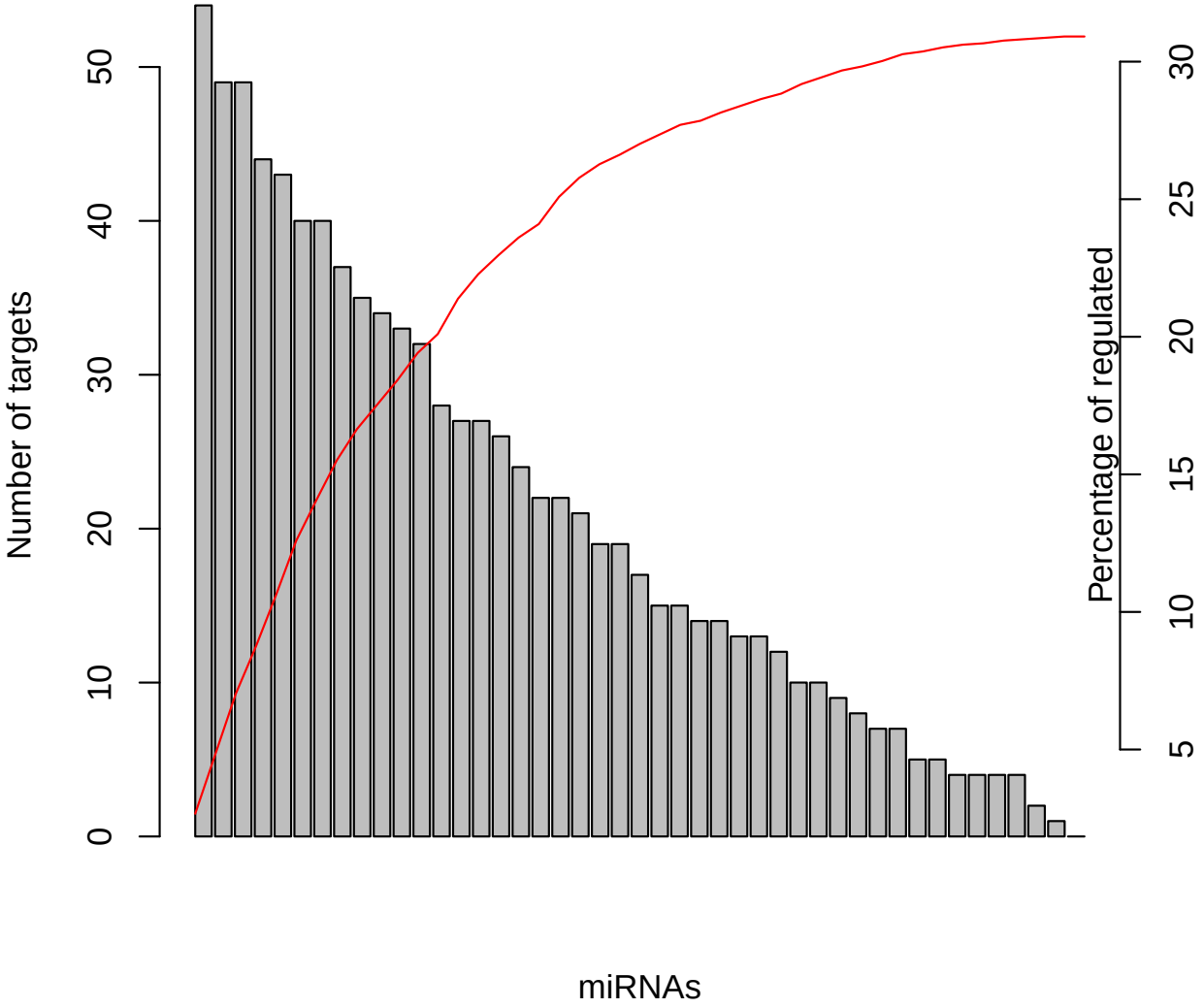

Figure 9: Barplot showing the number of targets per miRNA. The red line represents the cumulative percentage of mRNAs –respect to the total number of deregulated mRNAs– that the miRNAs are targeted by at least one miRNA.

```
corObject with:
 miRNA slot with 12 samples and 1733 probesets
 mRNA slot with 12 samples and 18900 probesets
Computations done:
- Differential expression mRNA:  limma method used
                                 DvH comparison used
- Differential expression miRNA:  limma method used
                                  DvH comparison used
- Correlation:  "pearson" method used
                "correlation" function used
                12 samples used
                45 miRNAs used
                   adj.pval < 0.05
                2025 mRNAs used
                   abs(logratio) > 0.58; abs(FC) > 1.5; adj.pval < 0.05
- Database:  "microCosm_v5_18" database used
```

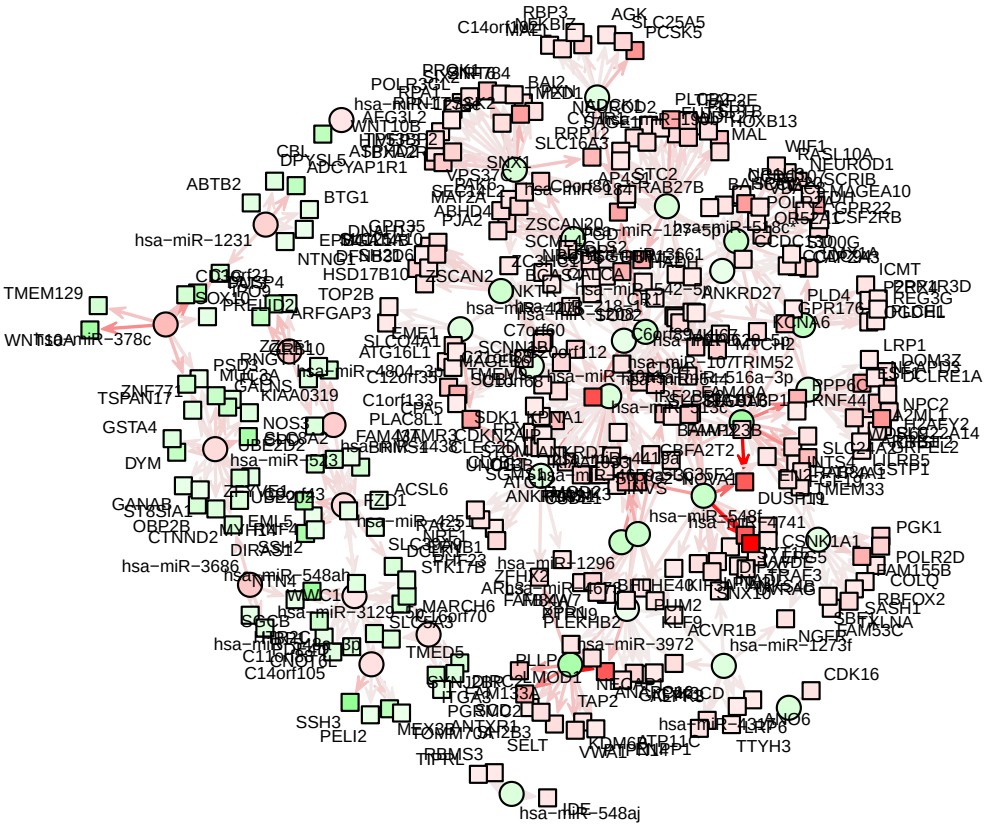

Figure 10: Network

```
 - Database:  "targetScan_v6.2_18" database used
- P.value adjustment:  "BH" method used
```

A pdf report can also be generated with the following function:

```
> mkReport(data.obj,"NameOfTheReport")
```

And then the file `NameOfTheReport.pdf` will be created.

7 Available databases

All `names` are from miRBase version 17. See `miRData` package for more information.

7.1 microCosm

`http://www.ebi.ac.uk/enright-srv/microcosm/htdocs/targets/v5/`

```
> data(microCosm_v5_18)
> head(microCosm_v5_18)
```

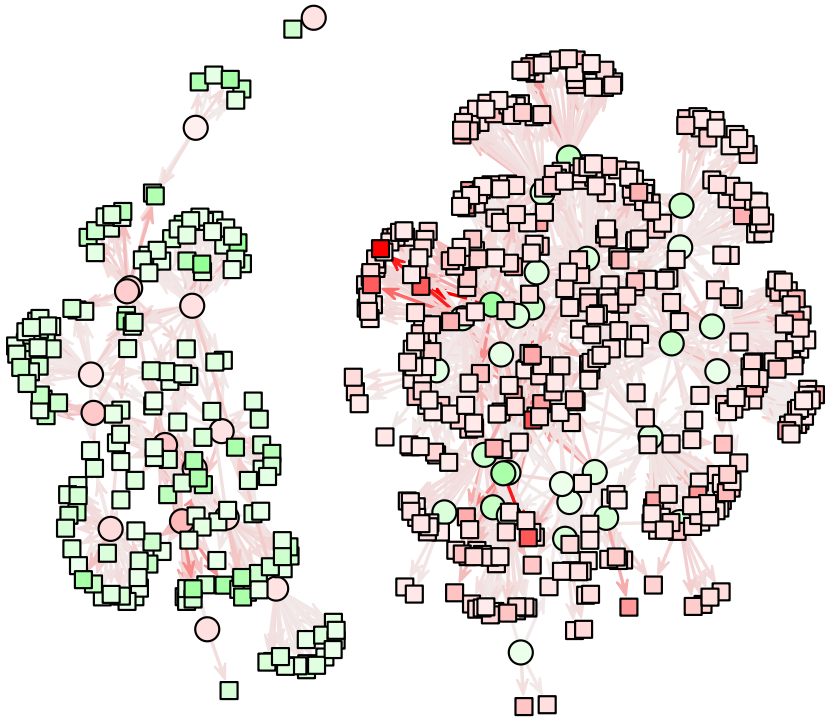

Figure 11: Network, bigger picture (without names)

	mir18	mir17	mir_acc	mirmicrocosm
hsa-miR-598:A1L4H1_HUMAN	hsa-miR-598	hsa-miR-598	MIMAT0003266	hsa-miR-598
hsa-miR-181a:NR6A1	hsa-miR-181a-5p	hsa-miR-181a	MIMAT0000256	hsa-miR-181a
hsa-miR-181c:NR6A1	hsa-miR-181c-5p	hsa-miR-181c	MIMAT0000258	hsa-miR-181c
hsa-miR-181b:NR6A1	hsa-miR-181b-5p	hsa-miR-181b	MIMAT0000257	hsa-miR-181b
hsa-miR-181d:NR6A1	hsa-miR-181d	hsa-miR-181d	MIMAT0002821	hsa-miR-181d
hsa-miR-212:NP_055530.2	hsa-miR-212-3p	hsa-miR-212	MIMAT0000269	hsa-miR-212

	target_name	target_entrezid	pval	score
hsa-miR-598:A1L4H1_HUMAN	A1L4H1_HUMAN	ENST00000389623	1.07251e-16	18.1954
hsa-miR-181a:NR6A1	NR6A1	ENST00000373584	1.99162e-13	20.0243
hsa-miR-181c:NR6A1	NR6A1	ENST00000373584	1.99162e-13	19.1021
hsa-miR-181b:NR6A1	NR6A1	ENST00000373584	1.99162e-13	18.7798
hsa-miR-181d:NR6A1	NR6A1	ENST00000373584	1.99162e-13	18.4404
hsa-miR-212:NP_055530.2	NP_055530.2	ENST00000310343	5.45163e-13	16.3193

	method	names
hsa-miR-598:A1L4H1_HUMAN	microcosm	hsa-miR-598:A1L4H1_HUMAN
hsa-miR-181a:NR6A1	microcosm	hsa-miR-181a:NR6A1

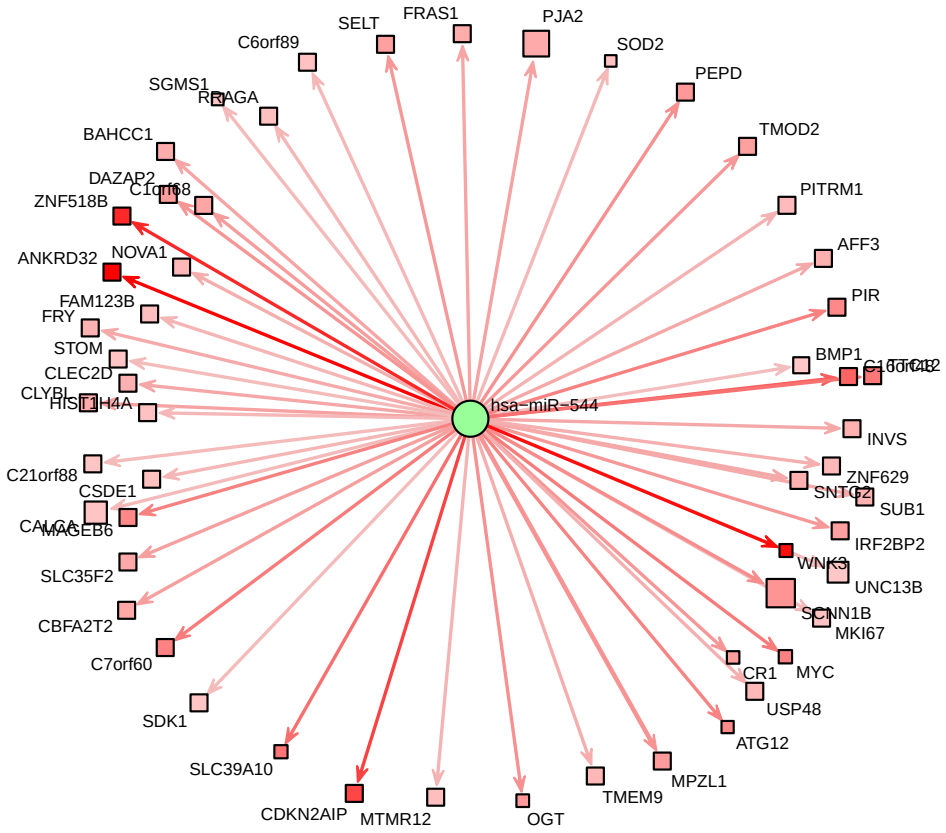

Figure 12: Targets of the miRNA hub. The size of the mRNAs reflects the number of protein-protein interactions they have (provided by `interact.table`).

```
hsa-miR-181c:NR6A1       microcosm       hsa-miR-181c:NR6A1
hsa-miR-181b:NR6A1       microcosm       hsa-miR-181b:NR6A1
hsa-miR-181d:NR6A1       microcosm       hsa-miR-181d:NR6A1
hsa-miR-212:NP_055530.2  microcosm  hsa-miR-212:NP_055530.2
```

7.2 targetScan

`http://www.targetscan.org/`

```
> data(targetScan_v6.2_18)
> head(targetScan_v6.2_18)
```

```
                        mir18      mir17      mir_acc mirtargetscan
hsa-let-7a:DZIP1  hsa-let-7a-5p hsa-let-7a MIMAT0000062    hsa-let-7a
hsa-let-7a:TEX261 hsa-let-7a-5p hsa-let-7a MIMAT0000062    hsa-let-7a
hsa-let-7a:CAP1   hsa-let-7a-5p hsa-let-7a MIMAT0000062    hsa-let-7a
hsa-let-7a:GIPC1  hsa-let-7a-5p hsa-let-7a MIMAT0000062    hsa-let-7a
```

```
hsa-let-7a:SUCLG2 hsa-let-7a-5p hsa-let-7a MIMAT0000062    hsa-let-7a
hsa-let-7a:CANT1  hsa-let-7a-5p hsa-let-7a MIMAT0000062    hsa-let-7a
                  target_name target_entrezid     method             names
hsa-let-7a:DZIP1        DZIP1           22873 targetscan  hsa-let-7a:DZIP1
hsa-let-7a:TEX261      TEX261          113419 targetscan hsa-let-7a:TEX261
hsa-let-7a:CAP1          CAP1           10487 targetscan   hsa-let-7a:CAP1
hsa-let-7a:GIPC1        GIPC1           10755 targetscan  hsa-let-7a:GIPC1
hsa-let-7a:SUCLG2      SUCLG2            8801 targetscan hsa-let-7a:SUCLG2
hsa-let-7a:CANT1        CANT1          124583 targetscan  hsa-let-7a:CANT1
```

8 Session Info

- R version 3.1.1 (2014-07-10), `x86_64-pc-linux-gnu`
- Locale: `LC_CTYPE=ca_ES.UTF-8`, `LC_NUMERIC=C`, `LC_TIME=ca_ES.UTF-8`, `LC_COLLATE=C`, `LC_MONETARY=ca_ES.UTF-8`, `LC_MESSAGES=ca_ES.UTF-8`, `LC_PAPER=ca_ES.UTF-8`, `LC_NAME=C`, `LC_ADDRESS=C`, `LC_TELEPHONE=C`, `LC_MEASUREMENT=ca_ES.UTF-8`, `LC_IDENTIFICATION=C`
- Base packages: base, datasets, grDevices, graphics, grid, methods, parallel, splines, stats, utils
- Other packages: AnnotationDbi˜1.26.1, Biobase˜2.24.0, BiocGenerics˜0.10.0, Category˜2.30.0, DBI˜0.3.1, DESeq˜1.16.0, Formula˜1.1-2, GO.db˜2.14.0, GOstats˜2.30.0, GenomeInfoDb˜1.0.2, Hmisc˜3.14-6, Matrix˜1.1-4, RSQLite˜1.0.0, RamiGO˜1.10.0, RankProd˜2.36.0, ReactomePA˜1.8.1, VennDiagram˜1.6.9, WriteXLS˜3.5.1, circlize˜0.1.3, gplots˜2.15.0, graph˜1.42.0, gsubfn˜0.6-6, gtools˜3.4.1, lattice˜0.20-29, limma˜3.20.9, locfit˜1.5-9.1, miRComb˜0.6.4, miRData˜0.4, network˜1.10.2, org.Hs.eg.db˜2.14.0, proto˜0.3-10, scatterplot3d˜0.3-35, survival˜2.37-7, xtable˜1.7-4
- Loaded via a namespace (and not attached): AnnotationForge˜1.6.1, DO.db˜2.8.0, DOSE˜2.2.1, GOSemSim˜1.22.0, GSEABase˜1.26.0, GlobalOptions˜0.0.4, IRanges˜1.22.10, KernSmooth˜2.23-13, MASS˜7.3-33, RBGL˜1.40.1, RColorBrewer˜1.0-5, RCurl˜1.95-4.4, RCytoscape˜1.14.0, Rcpp˜0.11.3, XML˜3.98-1.1, XMLRPC˜0.3-0, acepack˜1.3-3.3, annotate˜1.42.1, bitops˜1.0-6, caTools˜1.17.1, cluster˜1.15.2, colorspace˜1.2-4, digest˜0.6.4, foreign˜0.8-61, gdata˜2.13.3, genefilter˜1.46.1, geneplotter˜1.42.0, ggplot2˜1.0.0, graphite˜1.10.1, gtable˜0.1.2, igraph˜0.7.1, latticeExtra˜0.6-26, munsell˜0.4.2, nnet˜7.3-8, plyr˜1.8.1, png˜0.1-7, qvalue˜1.38.0, reactome.db˜1.48.0, reshape2˜1.4, rpart˜4.1-8, scales˜0.2.4, stats4˜3.1.1, stringr˜0.6.2, tcltk˜3.1.1, tools˜3.1.1

References

[1] Affò S., Dominguez M., Lozano JJ., Sancho-Bru P., Rodrigo-Torres D., Morales-Ibanez O., Moreno M., Millán C., Loaeza del Castillo˜A., Altamirano J., García-Pagán J.C., Arroyo V., Ginès P, Caballería J, Schwabe RF., and Bataller R. Transcriptome analyisis identifies TNF superfamily receptors as potential therapeutic targets in alcoholic hepatitis. *Gut*, 2012.

[2] Paul Shannon, Andrew Markiel, Owen Ozier, Nitin˜S. Baliga, Jonathan˜T. Wang, Daniel Ramage, Nada Amin, Benno Schwikowski, and Trey Ideker. Cytoscape: A software environment for integrated models of biomolecular interaction networks. *Genome Research*, 13(11):2498–2504, November 2003.